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Choosing Between Atezolizumab-Bevacizumab and STRIDE in First-Line Advanced Hepatocellular Carcinoma

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Abstract: ***Background: First-line systemic therapy for advanced hepatocellular carcinoma (HCC) has shifted toward immune-based combinations, particularly Atezolizumab plus Bevacizumab and the STRIDE regimen (single-dose Tremelimumab plus Durvalumab). Selecting between these regimens remains a common clinical challenge. Evidence Base: IMbrave150 demonstrated significant improvements in overall survival, progression-free survival, and response rates with Atezolizumab plus Bevacizumab versus Sorafenib. HIMALAYA demonstrated overall survival benefit with STRIDE, with durable long-term survival in a subset of patients. Differences in eligibility criteria, patient populations, and trial design limit direct comparison. Comparative Interpretation: Atezolizumab plus Bevacizumab appears preferable when rapid tumour response and progression control are priorities and anti-VEGF therapy is safe. STRIDE offers a VEGF-free alternative, particularly relevant for patients with bleeding risk or contraindications to Bevacizumab. Clinical Selection: Treatment selection should consider liver reserve, portal hypertension, bleeding risk, autoimmune disease, transplant context, and therapeutic goals. Conclusion: Both regimens are clinically important first-line options. Optimal treatment selection should be individualized according to patient characteristics, disease biology, and treatment feasibility.***

Keywords: Hepatocellular carcinoma; advanced HCC; atezolizumab; bevacizumab; tremelimumab; durvalumab; STRIDE regimen; immunotherapy; first-line systemic therapy

1. Introduction

For more than a decade after the SHARP trial, Sorafenib defined first-line systemic therapy for advanced hepatocellular carcinoma (HCC) by virtue of being the only positive option, not by virtue of being a good one.[1] Lenvatinib achieved non-inferiority in REFLECT and improved several secondary endpoints, but the multikinase era never delivered the durable benefit that patients with cirrhosis and a competing liver disease trajectory genuinely required.[2] The arrival of immune-based combinations changed this picture, and two regimens now dominate first-line discussion. Atezolizumab plus Bevacizumab, evaluated in IMbrave150, brought the first survival advantage of meaningful magnitude.[3,4] A few years later, the STRIDE regimen - a single 300 mg priming dose of Tremelimumab followed by regular-interval Durvalumab - emerged from HIMALAYA with a different efficacy signature.[5,6]

Advanced HCC is unlike most solid tumours because it almost always sits inside a diseased liver. Cirrhosis, portal hypertension, oesophagogastric varices, hepatitis B or C, alcohol-related liver disease, and metabolic dysfunction-associated steatohepatitis (MASH; formerly NASH) collectively shape what is tolerable, what is feasible, and what ultimately determines mortality.[7,8] Liver-related death frequently competes with cancer-related death, and a regimen that controls the tumour but precipitates variceal haemorrhage or hepatic decompensation has not necessarily helped the patient. This biological complexity is the reason cross-trial comparisons in HCC are tempting but hazardous.

IMbrave150 and HIMALAYA were positive phase III trials against the same comparator, but with materially different populations, eligibility filters, geographic distributions, and assessment schedules.[3–6] Forest plots and median survival numbers invite the reader to rank them; the trial designs themselves do not support that exercise. The argument advanced here is that Atezolizumab-Bevacizumab and STRIDE are not interchangeable immunotherapy combinations but biologically distinct strategies - one yoking PD-L1 blockade to vascular normalisation, the other using a single CTLA-4 priming dose to seed a deeper T-cell repertoire under sustained PD-L1 blockade. The clinical question, accordingly, is no longer which trial won, but which mechanism best fits the patient in front of the clinician.

Search methodology

A structured narrative literature search was performed using PubMed/MEDLINE, Embase, and major oncology conference proceedings up to May 2026. Search terms included hepatocellular carcinoma, advanced HCC, Atezolizumab, Bevacizumab, Tremelimumab, Durvalumab, STRIDE, IMbrave150, HIMALAYA, first-line systemic therapy, immunotherapy, anti-VEGF therapy, and sequencing. Pivotal phase III trials, updated survival analyses, patient-reported outcome studies, international guideline documents, landmark translational studies, and relevant real-world evidence reports were preferentially selected. Additional articles were identified from bibliographies of key publications and guideline documents. Because this is a narrative review, formal meta-analysis and risk-of-bias assessment were not performed.

2. Review

2.1 Trial Architecture and Eligibility

IMbrave150 randomised 501 patients with previously untreated unresectable HCC and Child-Pugh A liver function in a 2:1 ratio to Atezolizumab 1200 mg plus Bevacizumab 15 mg/kg every three weeks versus Sorafenib 400 mg twice daily.[3] Mandatory upper gastrointestinal endoscopy within six months of enrolment, with appropriate treatment of varices at risk of bleeding, was a defining design feature. Patients with untreated or incompletely treated oesophageal or gastric varices, recent variceal haemorrhage within six months, history of clinically significant bleeding, or major thromboembolic events were excluded. Approximately 38% of enrolled patients had macrovascular invasion or extrahepatic spread; hepatitis B was the dominant etiology, reflecting the Asia-Pacific weighting of recruitment.

HIMALAYA randomised 1171 patients with unresectable HCC and Child-Pugh A liver function - but no main portal vein invasion (Vp4) - to three arms: STRIDE (Tremelimumab 300 mg single dose with Durvalumab 1500 mg every four weeks), Durvalumab monotherapy 1500 mg every four weeks, or Sorafenib.[5] Mandatory variceal screening was not required, and Bevacizumab-related bleeding constraints did not apply. Etiology was more balanced - hepatitis B (~31%), hepatitis C (~27%), and non-viral causes (~42%) each contributed meaningfully - and the trial enrolled across the Americas, Europe, and Asia. The sorafenib comparator was identical in both trials, but exposure duration, subsequent therapy patterns, and ethnic distribution differed substantively.

These design-level differences are not bookkeeping; they directly shape who each trial's results apply to. A patient excluded from IMbrave150 because of uncontrolled varices is precisely the patient for whom STRIDE may be appropriate. Reading the two trials as if they enrolled the same population obscures this. Table 1 summarises the design contrasts.

Table 1: Design-level differences between IMbrave150 and HIMALAYA

Feature	IMbrave150	Himalaya	Clinical Implication
Design	Open-label phase III; 2:1 randomisation	Open-label phase III; four arms (STRIDE, Durvalumab, Sorafenib; Tremelimumab monotherapy arm discontinued)	Both pivotal and powered for OS
Sample size	501	1171 (STRIDE 393; Durvalumab 389; Sorafenib 389)	HIMALAYA larger, with broader subgroup precision
Control arm	Sorafenib 400 mg twice daily	Sorafenib 400 mg twice daily	Same benchmark, different control exposure
Child-Pugh	A only	A only	Neither informs B/C management
ECOG performance status	0-1	0-1	Excludes frail patients
Macrovascular invasion	Permitted; ~38% had MVI or extrahepatic spread	Vp4 (main portal vein) excluded	STRIDE evidence weaker for Vp4 disease
Variceal screening	Mandatory endoscopy within 6 months; varices at risk required treatment	Not mandated	Atezo-Bev requires endoscopy infrastructure
Bleeding and thrombotic exclusions	Strict: recent bleed, major thromboembolism excluded	Less restrictive	STRIDE feasible where bevacizumab is unsafe
Etiology mix	HBV ~49%, HCV ~21%, non-viral ~30%	HBV ~31%, HCV ~27%, non-viral ~42%	HIMALAYA more representative of Western and non-viral HCC
Geographic distribution	Asia-Pacific dominant	Global	Generalisability differs
Treatment regimen	Atezolizumab 1200 mg + Bevacizumab 15 mg/kg every 3 weeks	Tremelimumab 300 mg ×1 + Durvalumab 1500 mg every 4 weeks	Different mechanisms and toxicity profiles
Imaging schedule	Every 6 weeks (first 54 weeks)	Every 8 weeks	Affects PFS comparability

2.2 Efficacy

In the IMbrave150 primary analysis, Atezolizumab-Bevacizumab improved overall survival versus Sorafenib (hazard ratio 0.58; 95% CI 0.42-0.79; P<0.001), with co-primary improvement in independently assessed progression-free survival (hazard ratio 0.59; 95% CI 0.47-0.76; P<0.001).[3] The updated analysis at 15.6 months of additional follow-up reported median overall survival of 19.2 versus 13.4 months and confirmed an objective response rate of approximately 30% by independent review under RECIST 1.1, with an additional response signal under modified RECIST.[4] Disease control was achieved early; the Kaplan-Meier curves separated within the first months. This early divergence is consistent with the dual mechanism - VEGF blockade rapidly normalises tumour vasculature and shifts the immune microenvironment, while PD-L1 inhibition lifts the brake on tumour-reactive T cells.[9,10]

HIMALAYA showed STRIDE versus Sorafenib with median overall survival of 16.4 versus 13.8 months and a hazard ratio of 0.78 (96.02% CI 0.65-0.93).[5] The objective response rate was approximately 20%, and progression-free survival did not differ significantly between STRIDE and sorafenib. The notable feature of HIMALAYA is the survival tail. The 4-year update (Sangro and colleagues, 2024) reported persistent

separation of the curves, with 48-month overall survival rates of 25.2% versus 15.1% - a pattern more familiar from melanoma and renal-cell carcinoma than from HCC, and confirmed in 5-year follow-up showing 19.6% versus 9.4% survival.[6],[11] This plateau likely reflects deep T-cell repertoire expansion from CTLA-4 priming combined with ongoing PD-L1 blockade, even though Tremelimumab is administered only once. Durvalumab monotherapy in HIMALAYA was non-inferior to Sorafenib but did not match STRIDE, an internally informative result that suggests the priming dose - not PD-L1 inhibition alone - drives the durability.

Two clinical phenotypes therefore emerge from the evidence base, not one. Atezolizumab-Bevacizumab produces earlier and more frequent objective response with a progression-free survival advantage unmatched among current first-line regimens tested against sorafenib. STRIDE produces a delayed but durable survival benefit in a definable subset. Response matters when the tumour is threatening the portal vein or pressing on a biliary structure; durability matters when liver reserve must be protected over years. These are different goals, and both are legitimate. Patient-reported outcome analyses from both trials add a relevant dimension: Atezolizumab-Bevacizumab delayed deterioration in quality-of-life and disease-specific symptom scores versus sorafenib in IMbrave150,[12] and STRIDE preserved health-related quality of life in HIMALAYA without the symptomatic burden characteristic of multikinase therapy.[13]

Table 2: Efficacy outcomes across pivotal first-line studies

Trial	Regimen	Median OS (mo)	HR for OS (95% CI)	Median PFS (mo)	HR for PFS	ORR (%)	Key interpretation
IMbrave150 (primary)[3]	Atezolizumab + bevacizumab vs sorafenib	NR vs 13.2	0.58 (0.42-0.79)	6.8 vs 4.3	0.59 (0.47-0.76)	27 vs 12	Co-primary OS and PFS positive
IMbrave150 (updated)[4]	Atezolizumab + bevacizumab vs sorafenib	19.2 vs 13.4	0.66 (0.52-0.85)	6.9 vs 4.3	0.65 (0.53-0.81)	30 vs 11	Sustained early separation; PFS advantage maintained
HIMALAYA (primary)[5]	STRIDE vs sorafenib	16.4 vs 13.8	0.78 (0.65-0.93)*	3.8 vs 4.1	0.90 (0.77-1.05)	20.1 vs 5.1	OS positive; emerging survival tail
HIMALAYA (4-yr update)[6]	STRIDE vs sorafenib	-	0.78 (0.67-0.92)	-	-	48-mo OS 25.2% vs 15.1%	Confirmed durable benefit in a subset
HIMALAYA (5-yr update)[11]	STRIDE vs sorafenib	-	0.76 (0.65-0.89)	-	-	60-mo OS 19.6% vs 9.4%	Longest phase III follow-up in HCC
REFLECT (context)[2]	Lenvatinib vs sorafenib	13.6 vs 12.3	0.92 (0.79-1.06)	7.4 vs 3.7	0.66 (0.57-0.77)	24 vs 9	Non-inferior to sorafenib

2.3 Toxicity and Treatment-Limiting Issues

Toxicity profiles diverge along mechanistic lines. With Atezolizumab-Bevacizumab, the dominant safety considerations are Bevacizumab-attributable: hypertension, proteinuria, bleeding (notably variceal haemorrhage in cirrhosis), thromboembolic events, and impaired wound healing.[3],[4] Atezolizumab contributes the customary immune-mediated adverse events - hepatitis, colitis, pneumonitis, endocrinopathies - but in IMbrave150 these were generally manageable and did not dominate the safety narrative. A variceal bleed is not a minor toxicity signal in cirrhosis; it can define the treatment choice. The mandatory endoscopy protocol of IMbrave150 was not a research formality but a clinical requirement that must be reproduced in practice.

STRIDE shifts the toxicity emphasis to immune-related adverse events. Despite a single Tremelimumab dose, CTLA-4 blockade contributes recognisable risks - immune-mediated hepatitis, colitis, pneumonitis, dermatitis, and endocrinopathies - and a meaningful minority of patients require high-dose corticosteroids.[5],[6] The priming-dose design appears to limit cumulative CTLA-4 toxicity compared with full-schedule Ipilimumqb-based combinations but does not abolish it. Active autoimmune disease and the post-transplant setting remain relative contraindications. Immune-mediated hepatitis arising in a cirrhotic liver demands prompt recognition. Steroid access, infrastructure for immune-related adverse-event management, and clinician familiarity with corticosteroid escalation are therefore not optional adjuncts but prerequisites.

Table 3: Clinical toxicity trade-offs

Clinical issue	Atezolizumab + bevacizumab	STRIDE	Practical selection guidance
Bleeding and varices	Significant; mandatory endoscopy and variceal management	No bevacizumab-related risk; baseline cirrhotic bleeding risk persists	Untreated or high-risk varices favour STRIDE
Hypertension	Common; usually manageable	Uncommon	Pre-existing uncontrolled hypertension favours STRIDE
Proteinuria	Common; monthly monitoring required	Not characteristic	Chronic kidney disease with proteinuria favours STRIDE
Thromboembolism	Both arterial and venous risk increased	No specific increase reported	Recent arterial or venous thromboembolism favours STRIDE
Wound healing and planned surgery	Surgery must be deferred	Less restrictive	Planned intervention favours STRIDE
Immune-mediated hepatitis	Reported but moderate frequency	Higher rate; particular vigilance in cirrhotic liver	Pre-existing autoimmune hepatitis - case-by-case decision

Colitis	Reported	Higher rate, particularly after priming dose	History of inflammatory bowel disease - cautious use of either
Endocrinopathies	Thyroid most common	Thyroid, hypophysitis, adrenalitis	Endocrinology access essential for STRIDE
Steroid availability	Less frequent escalation	Steroid escalation pathway essential	Limited steroid access argues against STRIDE
Transplant context	Caution	Generally contraindicated	Bridge-to-transplant requires hepatology discussion
Active autoimmune disease	Caution	Generally contraindicated	STRIDE typically avoided

2.4 Patient Selection Framework

The practical question is not which trial won, but which patient can safely receive anti-VEGF therapy and whose disease justifies waiting for an immune-mediated tail. The framework below organises selection around the clinical questions a tumour board actually asks.

(A) Patients Well Suited to Atezolizumab-Bevacizumab

Atezolizumab-Bevacizumab is the appropriate first-line choice when tumour shrinkage is clinically valuable - for symptomatic or rapidly progressive disease, large intrahepatic lesions threatening liver function, or pulmonary and nodal disease where the objective response rate matters. Eligibility presumes preserved liver function (Child-Pugh A; ALBI grade 1 preferred), absent or adequately treated varices on recent endoscopy, no recent bleeding, no significant proteinuria, controlled blood pressure, and no major arterial event in the preceding six months. Patients with macrovascular invasion short of Vp4 are also reasonable candidates, since rapid disease control may protect liver function from tumour-driven decompensation.

(B) Patients Better Suited To Stride

STRIDE is preferred when bleeding risk dominates the picture: untreated or high-risk varices, recent gastrointestinal haemorrhage, or contraindications to Bevacizumab including significant proteinuria, uncontrolled hypertension, recent thromboembolism, or planned surgery. In addition, STRIDE is attractive when durable immune control rather than short-term response is the priority - for example, lower-burden disease with stable hepatic reserve where the late survival plateau is of substantial clinical value. STRIDE is also more feasible in settings where endoscopic infrastructure for routine variceal surveillance is limited, although this advantage is offset by the parallel requirement for immune-related adverse-event infrastructure. The signal from earlier pooled analyses that non-viral HCC may respond less well to PD-1/PD-L1 monotherapy has not been clearly reproduced in subgroup analyses of HIMALAYA, and should not be used as a rigid decision rule.[14]

(C) Patients for Whom Neither Regimen Is Ideal

Several scenarios place a patient outside the evidence base for both regimens. These include Child-Pugh B or C disease (excluded from both pivotal trials), Eastern Cooperative Oncology Group performance status of 2 or worse, active autoimmune disease requiring systemic immunosuppression, solid organ transplant recipients (in whom checkpoint inhibition carries high rejection risk), decompensated cirrhosis with ascites, encephalopathy or jaundice, recent major bleeding, and uncontrolled active infection. In these patients, decisions should be individualised, often in favour of tyrosine kinase inhibitor monotherapy, Durvalumab alone (non-inferior to Sorafenib in HIMALAYA), best supportive care, or clinical trial enrolment. Real-world studies of Atezolizumab-Bevacizumab in Child-Pugh B disease report acceptable but inferior outcomes and a higher rate of liver-related events, and should not be extrapolated as routine practice.[15]

Table 4: Practical first-line selection scenarios

Clinical scenario	Preferred option	Rationale	Caveat
Child-Pugh A, varices treated or absent, no bleeding risk, high-burden disease	Atezolizumab + Bevacizumab	Best ORR and PFS; early disease control	Confirm recent endoscopy and acceptable blood pressure/proteinuria
Child-Pugh A, untreated or high-risk varices, recent variceal haemorrhage	STRIDE	Avoids bevacizumab-related bleeding risk	Monitor for irAEs; ensure steroid access
Significant proteinuria, uncontrolled hypertension, or recent thromboembolism	STRIDE	Bevacizumab contraindicated	Caution if autoimmune history
MASH/NASH etiology with modest disease burden	STRIDE reasonable	Durable survival tail observed; etiology-based exclusion not supported by HIMALAYA subgroups	Consider Atezo-Bev if early shrinkage required
Macrovascular invasion (non-Vp4) with preserved liver function	Atezolizumab + Bevacizumab	Rapid response may protect liver	Endoscopy and BP control mandatory
Vp4 main portal vein invasion	Atezo-Bev with caution, or clinical trial	STRIDE excluded such patients; Atezo-Bev evidence stronger here	Multidisciplinary review essential
Active autoimmune disease or solid organ transplant	Neither (consider TKI, trial, or supportive care)	Both regimens carry immune-mediated risks	Specialist multidisciplinary discussion
Child-Pugh B7 in an otherwise fit patient	Off-trial individualised decision; Durvalumab monotherapy or TKI	Pivotal trials excluded this population; real-world data evolving	Lower threshold to reassess at first sign of decompensation
Limited endoscopic infrastructure	STRIDE if affordable	No mandatory variceal screening	Cost remains a major barrier

2.5 Biology and Mechanism

The mechanistic contrast explains why the two regimens produce different clinical phenotypes. Bevacizumab does more than starve a tumour of its vasculature. VEGF is immunosuppressive - it impairs dendritic cell maturation, expands myeloid-derived suppressor cells and regulatory T cells, and inhibits effector T-cell trafficking through dysfunctional endothelium.[9],[10] Anti-VEGF therapy normalises tumour vasculature, restores T-cell infiltration, and reduces VEGF-driven immunosuppression. Combined with PD-L1 blockade, the result is rapid restoration of an effector immune response within an HCC microenvironment that is, by default, hostile to T-cell function. The early objective response and progression-free survival advantage of Atezolizumab-Bevacizumab is the clinical readout of this synergy.

STRIDE rests on a different premise. A single high dose of Tremelimumab provides transient but substantive CTLA-4 blockade at therapy initiation, expanding the T-cell repertoire and lowering the activation threshold for tumour-reactive clones. Sustained Durvalumab then maintains PD-L1 blockade across the long arc of treatment.[5],[6] This biological logic predicts a delayed kinetic of benefit - the response rate is lower and the early curves do not separate dramatically - but a subset of patients develops durable immune control that translates into a late survival plateau. The internally informative comparison with Durvalumab monotherapy in HIMALAYA, which did not match STRIDE, supports the contribution of the priming dose. Reduced to a clinical formula: VEGF-PD-L1 synergy buys breadth and speed; CTLA-4 priming with sustained PD-L1 blockade buys depth and durability.

2.6 Real-World Considerations and the Lmic Perspective

The Indian and broader low- and middle-income country (LMIC) context reframes the discussion. Hepatitis B remains the dominant etiology across much of Asia and sub-Saharan Africa; hepatitis C, alcohol-related disease, and MASH each contribute meaningfully; and a substantial fraction of patients present with advanced disease and significant portal hypertension.[7],[8] Cost and reimbursement constraints are not peripheral concerns. Atezolizumab and Bevacizumab in combination, and Tremelimumab-Durvalumab as the STRIDE regimen, both remain expensive and unevenly accessible. In public-sector practice across many LMICs, generic tyrosine kinase inhibitors continue to be first-line by economic necessity rather than scientific preference.

Where immunotherapy is feasible, infrastructure becomes the deciding variable. Atezolizumab-Bevacizumab demands routine upper gastrointestinal endoscopy with banding or pharmacologic prophylaxis as indicated; this is straightforward in tertiary centres but uneven across district hospitals. STRIDE removes that requirement but shifts the burden to immune-related adverse-event recognition and management, including timely access to high-dose corticosteroids, endocrinology support, and gastroenterology backup for steroid-refractory colitis or hepatitis. Neither regimen is a low-infrastructure option.

Sequencing also matters more in LMIC practice, where second-line therapy may be constrained by both finance and toxicity tolerance. The first-line choice cannot be made in isolation from what will be available at progression. Large real-world cohorts of Atezolizumab-Bevacizumab from Asian and European centres have broadly reproduced trial outcomes in carefully selected patients, although attrition from bleeding and hepatic decompensation occurs in those with marginal liver reserve.[16],[17] Comparable real-world series for STRIDE are still maturing. The phase IIIb AMETHISTA trial and emerging post-marketing experience will be informative.[18]

2.7 Sequencing After Progression

Sequencing after first-line immunotherapy in advanced HCC remains evidence-light. No randomised trial has defined the optimal second-line strategy after either Atezolizumab-Bevacizumab or STRIDE. Several tyrosine kinase inhibitors - Lenvatinib, Sorafenib, Regorafenib, Cabozantinib - are used in this setting based on extrapolation from post-Sorafenib randomised data and accumulating retrospective series.[19–22] Ramucirumab remains the only agent with prospective randomised evidence specifically in patients with alpha-fetoprotein-high disease following first-line therapy.[23]

Two practical principles deserve emphasis. First, liver function at the moment of progression dictates feasibility; a patient who progresses with new ascites or rising bilirubin has fewer realistic options than one who progresses with stable ALBI grade. Second, the first-line choice constrains the second-line option set. After Atezolizumab-Bevacizumab, the rationale for further anti-VEGF exposure with Lenvatinib or Cabozantinib is straightforward; after STRIDE, a VEGF-pathway tyrosine kinase inhibitor is mechanistically attractive because it introduces a new mode of action. Rechallenge with checkpoint inhibitors, or switching to dual checkpoint regimens such as Nivolumab-Ipilimumab after STRIDE failure, remains hypothesis-generating and should generally be reserved for clinical trials.[24]

2.8 GUIDELINE POSITIONING

Current international guidelines from ASCO, ESMO, AASLD, and NCCN converge on Atezolizumab-Bevacizumab and Tremelimumab-Durvalumab (STRIDE) as preferred first-line options for suitable patients with unresectable HCC and Child-Pugh A liver function.[25–27] No major guideline declares either regimen universally superior. The 2024 ASCO update explicitly positions the two as alternatives selected on patient characteristics and contraindications, requiring variceal screening and management when Bevacizumab is used.[25] The 2025 ESMO Clinical Practice Guideline adopts a similar position, reflecting the convergence of evidence and the absence of head-to-head comparison.[26] The Barcelona Clinic Liver Cancer (BCLC) 2022 strategy similarly positions both immunotherapy options at the head of the BCLC stage C algorithm.[28] Lenvatinib and Sorafenib retain a role where immunotherapy is infeasible - through contraindication, cost, or patient preference.

2.9 Unresolved Questions

Several questions remain genuinely open and will shape the next decade of clinical research. Biomarker development is unsatisfying: tumour PD-L1 expression has not reliably predicted benefit in HCC, and alpha-fetoprotein, immune signatures, and VEGF signatures remain hypothesis-generating tools rather than decision-support instruments. Etiology-specific effects are unsettled - an earlier preclinical and clinical signal suggested attenuated PD-1/PD-L1 monotherapy benefit in MASH-HCC,[14] but subsequent analyses and the HIMALAYA dataset do not consistently support a hard etiology-based decision rule for combination immunotherapy.[6] Child-Pugh B disease remains under-served; both pivotal trials excluded it, and cohort data are heterogeneous.

Combination with locoregional therapy is moving rapidly: EMERALD-1 demonstrated improved progression-free survival when transarterial chemoembolisation was combined with Durvalumab and Bevacizumab in intermediate-stage disease,[29] and parallel trials are testing analogous combinations. Conversion therapy and downstaging to resection or transplantation using systemic immunotherapy is increasingly performed in tertiary practice but lacks prospective eligibility criteria. Real-world outcomes in Asian and LMIC populations, including HBV-dominant cohorts and patients with marginal liver reserve, require systematic prospective documentation. None of these gaps is closed by either IMbrave150 or HIMALAYA in isolation.

Conclusion

Atezolizumab-Bevacizumab remains a benchmark first-line regimen for advanced HCC where response rate, progression-free survival, and rapid disease control are the priorities - and where anti-VEGF therapy is demonstrably safe. STRIDE is not a fallback; it is a distinct VEGF-free immunotherapy strategy, particularly valuable when bleeding risk, untreated varices, or anti-VEGF contraindications dominate the picture, and one whose late survival plateau reflects something the multikinase era never delivered.

Cross-trial comparisons between IMbrave150 and HIMALAYA remain hypothesis-generating and should not be allowed to ossify into a hierarchy. The best first-line choice in advanced HCC is not trial-name loyalty but a clinical judgement about the liver, the tumour, and the patient in front of the clinician. The modern question is no longer whether HCC should be treated with immunotherapy, but which immune strategy best fits the liver, the tumour, and the patient before us.

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Consent
Not applicable since this is a review article.

Ethical Approval
Not applicable since this is a review article

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